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## Bullous systemic lupus erythematosus – a case report

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### ABSTRACT

Skin involvement in systemic lupus erythematosus (SLE) occurs in more than 75% of patients with this condition. Vesicles and blisters in lupus erythematosus (LE) may be present in SLE secondary to interface vacuolar changes in the epidermis, in discoid LE also secondary to vacuolar epidermal changes, and in bullous LE secondary to antibodies anti-collagen VII deposits with neutrophilic aggregates. In addition, blisters can occur due to the association of SLE with other autoimmune blistering diseases (e.g. bullous pemphigoid). BSLE is a rare blistering disease that mainly occurs in females (30–40 years old), and less frequently in children and adolescents. The most common presentation is rapid and widespread development of tense vesicles and bullae over erythematous macules or plaques. Preferential sites are: superior trunk, proximal superior limbs, and face (lips) with symmetrical distribution. Mucosal involvement is common on perioral, pharyngeal, laryngeal, and genital areas. The involvement of sun-exposed areas is not mandatory. The lesions usually progress with no scarring, but hypo or hyperchromia may be present. We report an 18-year-old female patient with blistering lesions at admission, who was diagnosed with BSLE. She was initially treated with systemic prednisone and hydroxychloroquine. Her condition evolved with relapsing lesions, which required the introduction of Dapsone. The authors emphasize the relevance of recognizing BSLE—a rare presentation of SLE—which may evolve with marked clinical presentation.

### Keywords

Lupus Erythematosus, Systemic, Blister, Dapsone, Diagnosis, Therapeutics

### INTRODUCTION

Skin involvement in systemic lupus erythematosus (SLE) occurs in more than 75% of patients with this condition. Vesicles and blisters in SLE may be detected in three different conditions: (1) due to an interface vacuolar dermatitis; (2) due to the association of SLE with other autoimmune blistering diseases (e.g. bullous pemphigoid); and (3) due to an autoimmune blistering disease related to antibodies anti-collagen

VII. This last condition refers to bullous systemic lupus erythematosus (BSLE).

BSLE is a rare blistering disease that mainly occurs in females (3–40 years old), and less frequently in children and adolescents.<sup>1-2</sup> The involvement of sun-exposed areas is not mandatory, and is marked by the rapid and widespread development of tense vesicles and bullae over erythematous macules or

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plaques. Preferential sites are: superior trunk, proximal superior limbs, and face (lips)<sup>3</sup> with symmetrical distribution. Mucosal involvement is common on perioral, pharyngeal, laryngeal, and genital areas. The lesions usually progress with no scarring, but hypo or hyperchromia may be present.

## CASE REPORT

An 18-year-old female was hospitalized presenting slightly painful and pruritic vesicles and bullae on the face, oral mucosa, abdomen, thighs, and dorsum over the last 2 weeks. She also reported weight loss, migratory polyarthralgia with morning stiffness longer than 30 minutes, myalgia, fatigue, fever, alopecia, and malar rash associated with photosensitivity over the last 2 months. She was taking medroxyprogesterone acetate every 3 months as a contraceptive method. Her past medical history included a pregnancy at the age of 17, with low titers in the Venereal Disease Research Laboratory test, and a negative treponemal test.

The admission clinical examination revealed a prostrated and pale patient, with normal vital signs. Skin findings showed the presence of a malar rash, and multiple tense vesicles and bullae varying from 1 mm to 6 cm, over erythematous macules and plaques (Figure 1). These lesions were present on the face, including eyelids, arms, abdomen, dorsum, and thighs. Involvement of the vermilion border of the lips and oral mucosa was present. No lymphadenopathy and



**Figure 1.** BSLE. Arciform and linear tense bullae of varying sizes over erythematous macules and plaques on abdomen, thighs (A) and dorsum (B). BSLE = bullous systemic lupus erythematosus.

signs of arthritis were detected; the remaining physical examination revealed no alterations.

BSLE was considered as the first hypothesis, followed by the differential diagnosis of other conditions, such as: epidermolysis bullosa acquisita, bullous pemphigoid, dermatitis herpetiformis, linear immunoglobulin (Ig)A bullous dermatosis, and drug eruption.

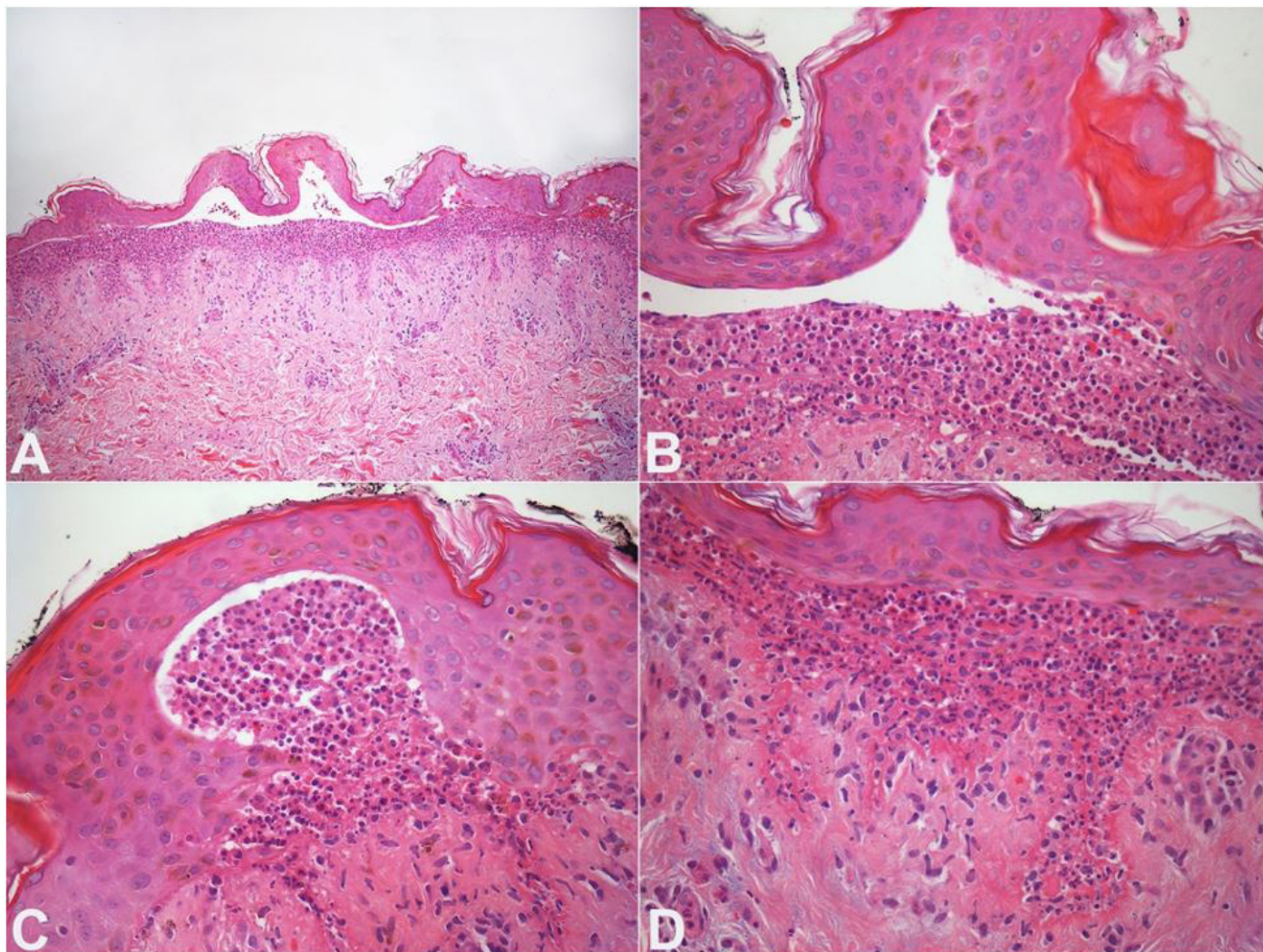
General laboratory evaluation showed a complete blood cell count with pancytopenia hemoglobin levels of 11.0 g/dL (reference range [RR]: 12.3–15.3 g/dL), leukocytes of 2880 per mm<sup>3</sup> (RR: 4.4–11.3 × 10<sup>3</sup>/mm<sup>3</sup>) and platelet count of 105,000 per mm<sup>3</sup> (RR: 150–400 × 10<sup>3</sup>/mm<sup>3</sup>). The direct Coombs assay was positive, but lactate dehydrogenase and bilirubin were at normal levels. Urinalysis revealed the presence of proteinuria, hematuria, and leukocyturia, with no casts. The spot urine protein/creatinine ratio was 856 mg/g (RR: < 300 mg/g). Renal function was preserved (creatinine of 0.63 mg/dL [RR: 0.4–1.3 mg/dL] and urea of 15 mg/dL [RR: 5–25 mg/dL]). Complement was at low levels, C3 < 21 mg/dL (RR: 67–149 mg/dL) and C4 = 7 mg/dL (RR: 10–38mg/dL); anti-nuclear antibody was positive (1/640) with a homogeneous nuclear pattern, anti-double-stranded DNA and anti-histone were positive.

Skin histopathology revealed subepidermal cleavage with a neutrophilic inflammatory infiltrate (Figure 2). Direct immunofluorescence (DIF) showed positivity for IgG at the basement membrane zone (BMZ) in a linear pattern (Figure 3A). Salt-split skin indirect immunofluorescence showed the presence of IgG deposits at the dermal side of cleavage (negative for IgA and IgM) (Figure 3B). ELISA was positive for antibodies against type VII collagen.

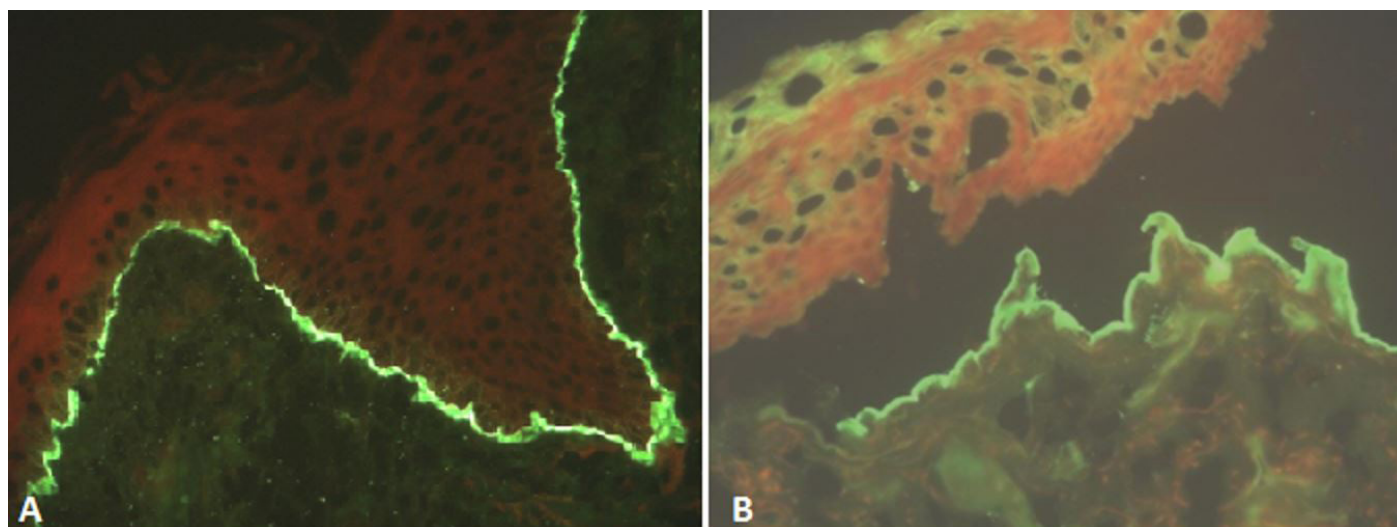
The clinical and laboratory findings confirmed the diagnosis of BSLE.

The patient was treated with oral prednisone 1 mg/kg/d along with hydroxychloroquine 400 mg/d 5 days per week. Skin lesions and other SLE symptoms markedly improved after 1 week of treatment and the patient was discharged. However, the skin lesions on the vermilion border of the lips, eyelids, forearms, dorsum, and thighs relapsed soon after, despite adherence to treatment. Hospitalization was necessary due to the extent of skin involvement and systemic symptoms. Dapsone 200 mg/d was added to the





**Figure 2.** BSLE. Skin histopathology. **A** – Subepidermal cleavage with neutrophils. The inflammatory cells are disposed along the papillary dermis; **B** – Subepidermal cleavage partially filled with neutrophils; **C** – Subepidermal blister with neutrophils and inflammatory cells at the periphery of the bulla; **D** – Neutrophils are present in the superficial dermis. Note the thickening of the basement membrane. (H&E, A: 100X; B, C, and D: 400X). BSLE = bullous systemic lupus erythematosus.



**Figure 3.** **A** – Direct immunofluorescence shows homogenous IgG deposit at the basement membrane zone (400X); **B** – Indirect immunofluorescence (salt-split skin), human foreskin substrate: IgG deposits at the dermal side of the split (400X).

**Table 1.** Modified diagnostic criteria for BSLE<sup>21</sup>

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1- Diagnosis of SLE according to the American College of Rheumatology
2- Vesicles and bullae arising upon but not limited to sun-exposed skin
3- Histopathology consistent with DH
4- Negative or positive indirect IF for circulating BMZ antibodies using separated skin as the substrate
5- DIF of lesional and non-lesional skin revealing linear or granular IgG and/or IgM and often IgA at the BMZ; if there is a linear pattern of Ig deposition, immunoelectron microscopy should be done to demonstrate the immune reactants below the basal lamina

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BMZ = basement membrane zone; BSLE = bullous systemic lupus erythematosus; DH = dermatitis herpetiformis; DIF = direct immunofluorescence; IF = indirect immunofluorescence; Ig = immunoglobulin; SLE = systemic lupus erythematosus.

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therapeutic regimen, with subsequent improvement of the clinical features. Hydroxychloroquine was withdrawn due to hemolysis.

## DISCUSSION

BSLE is a rare autoimmune blistering disorder that usually presents as tense bullae and/or vesicles in patients with a previously known or concurrent diagnosis of SLE. Due to the rarity of the disease, epidemiologic data are limited. A French study<sup>4</sup> showed an incidence of bullous skin disorders (excluding bullous pemphigoid) of 3.4 cases per million per year. The occurrence of BSLE among children and adolescents with SLE is around 1%.<sup>2</sup> Data on BSLE are scarce; therefore, the knowledge about the disease is mostly based on case reports or case series.

BSLE patients usually present with clinical features of SLE. The blisters predominantly occur on the face, neck, upper extremities, oral mucosa, and vermilion border. Development of bullae is triggered by sun exposure. Bullous lesions are tense and heal with no scarring.<sup>5-13</sup> Mucosal involvement features include either blisters or painless ulcers. Esophagitis dissecans was reported.<sup>14</sup> Differential diagnoses usually include other subepidermal bullous diseases such as bullous pemphigoid (BP), epidermolysis bullosa acquisita (EBA), linear IgA bullous dermatosis, and dermatitis herpetiformis (DH).<sup>15</sup>

The histopathology of BSLE usually shows a subepidermal bullae with neutrophil-predominant inflammatory infiltrate below the bullae formation. The presence of micro abscesses in the dermal papillae is also frequent, which makes the histopathology features of BSLE very similar to DH.<sup>16</sup> In BSLE, neutrophils tend to be in a dispersed arrangement (Figure 2C) and may extend into the papillary dermal collagen (Figure 2D).

Deposits of mucin are often seen in the deep dermis.<sup>17</sup> In counterpart, the neutrophilic infiltrate in DH is focal and localized at the papillary dermis.

The immunopathologic findings in BSLE include: direct immunofluorescence with linear IgG deposits at BMZ, and occasional granular IgA, IgM, and C3 deposits.<sup>17</sup> Salt-split skin indirect immunofluorescence reveals IgG deposition at the dermal side of cleavage, and is a helpful tool for BSLE.<sup>13</sup> The presence of autoantibodies against type VII collagen may be detected in patients with BSLE.<sup>18,19</sup>

Camisa and Sharma<sup>20</sup> were the first authors to establish diagnostic criteria for BSLE. In 1988, with the use of immunofluorescence, these diagnostic criteria were reviewed and are shown in Table 1.<sup>21,22</sup>

The current therapeutic regimens for BSLE are based on the pathogenesis of the disease, case-reports, and case-series. Dapsone is used as first-line therapy<sup>6,11,23-25</sup> along with glucocorticoids and immunosuppressants. Other therapeutic options include mycophenolate mofetil<sup>5,7,13,26</sup> methotrexate,<sup>27</sup> rituximab,<sup>28</sup> hydroxychloroquine and intravenous immunoglobulin.<sup>8</sup>

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